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VIEWPOINT

The art of facilitation: a delicate hormonal balance!

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The central respiratory pattern generator has inherent rhythmicity, but it is modulated on a breath-to-breath basis by integrated peripheral and central signals that modulate the pattern of respiratory motor efferent outflow and subsequent drive to the respiratory muscles. Despite the intensification of research into the modulation of the control of breathing by steroid hormones, many questions remain unanswered (Gargaglioni et al., 2019). There are striking sex differences in the prevalence of certain respiratory conditions such as asthma, sleep disordered breathing (SBD) and sudden unexpected death of an infant (SUDI), as well as in neuromuscular and neurodegenerative diseases such as muscular dystrophy and amyotrophic lateral sclerosis. In recent years, there is mounting evidence of intrinsic morphophysiological differences in the respiratory system between the sexes as a result of genetic and hormonal differences. Asthma, cystic fibrosis, SDB and SUDI are all associated with inflammation and dysbiosis, and fully elucidating the mechanisms underpinning the apparent sex differences remains difficult. Although differences in sex hormones are present throughout early life, the pattern of expression is most divergent from the onset of puberty with the establishment of the menstrual cycle in females and a rise in circulating testosterone in males. Once sexual maturation is established in females, 17β-oestradiol and progesterone express cyclical fluctuations with every menstrual cycle until menopause with recent publications suggesting that, similar to other systems, variability between consecutive menstrual cycles adds an additional level of complexity (McNulty et al., 2021).

The respiratory system is malleable to stressors, particularly within critical windows of development or other sensitive periods. Respiratory plasticity may be adaptive or maladaptive depending on the prevailing environment. One type of respiratory plasticity, termed phrenic long-term facilitation (pLTF), can be induced in rats following exposure to acute intermittent hypoxia (AIH). The facilitation of phrenic neural output translates into enhanced minute ventilation that has been demonstrated in behaving rodents and in humans (Keough et al., 2021; McGuire et al., 2004). The response to physiological stressors such as chemostimulation or exercise can reveal distinct physiological strategies between the sexes. For example, it was recently demonstrated that male and female healthy young adults exhibit hypercapnic AIH-induced ventilatory LTF via distinct routes (Keough et al, 2021). It is important that we explore integrative respiratory control in both sexes to further our understanding and strive to optimise therapeutic strategies in disease. Significant advances have been made in our understanding of the signalling pathways underpinning pLTF yet further delineating the systemic or microenvironmental conditions that hamper or facilitate respiratory plasticity will aid the ambition to harness AIH-induced pLTF as a therapeutic strategy.

In this issue of *Experimental Physiology*, Barok and colleagues report a persistent impairment of the capacity to express respiratory plasticity within ovariectomised rats assessed by way of AIH-induced pLTF (Barok et al., 2021). Ovariectomy is a common experimental approach to examine the influence of female sex hormones on physiological function. As with any longitudinal experimental design, the maturation at the time of the intervention, interventionally induced changes in body mass, and thereby, the selection of appropriate controls and the potential of redundancy within physiological systems can make interpretation of resulting data difficult. Beyond the gonads/ovaries, steroids have also been shown to be produced by multiple cell types in the zona reticularis of the adrenal gland, in

some neurons and glia, and at the level of the mitochondria, which prompted Barok et al. (2021) to investigate long-term hormonal status in ovariectomised female rats. The authors report that similar to 2 weeks' post-ovariectomy, at 12 weeks post-ovariectomy there was no significant compensatory recovery of circulating concentration of oestrogen in the 9-month-old female rats. Further analysis is required to determine the expression of other androgens.

The functional knock-on effects of ovariectomy extend beyond the elimination of sex steroid hormones and caution must be exercised when making direct associations. Steroid sex hormones are multifunctional proteins that modulate neurogenesis, dendritic growth, ion exchange, insulin-like growth factor and growth hormone, and serotonergic signalling, in addition to redox homeostasis and immune function. The physiological influence of the sex hormones does not simply depend on their concentration in circulation but extends to the location and subtype expression of the steroid receptors and the interaction between hormonal signalling pathways. Therefore, teasing apart the functional roles of sex steroids with hormone supplementation should employ physiological hormone concentrations and consider possible changes in receptor expression post-ovariectomy (Gargaglioni et al., 2019). Questions remain as to why plasticity is more easily expressed in middle-aged female rats compared to young female rats. Despite the increased capacity for pLTF expression in females in the presence of oestrogen, oestrogen is not required for pLTF expression in males. However, it is clear in female rats that removing the primary source of sex steroids undermines the expression of phrenic LTF, similar to previously identified inflammation-induced impairment. The study by Barok and colleagues paves the way for longitudinal studies in which the authors hope to examine the functional role of sex steroids on respiratory control, particularly at the level of the spinal respiratory motor nuclei.

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COMPETING INTERESTS

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